Chapter 2: *Haemophilus influenzae* type b Invasive Disease

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I. Disease description

Haemophilus influenzae (Hi) invasive disease is caused by the bacterium *Haemophilus influenzae*. Hi may be either encapsulated (typable) or unencapsulated (nontypable). Six antigenically distinct capsular types of Hi (types a-f) have been identified that can cause invasive disease among people. Nontypable strains may also cause invasive disease, but are less virulent than encapsulated strains and are rare causes of serious infection among children.

Invasive *H. influenzae* diseases include clinical syndromes of meningitis, bacteremia or sepsis, epiglottitis, pneumonia, septic arthritis, osteomyelitis, pericarditis, empyema, and abscesses. In contrast, syndromes of mucosal infections such as bronchitis, sinusitis, and otitis are considered noninvasive disease. The noninvasive syndromes are not nationally notifiable.

Before the introduction of effective vaccines, *Haemophilus influenzae* type b (Hib) was the cause of >95% of invasive Hi diseases among children <5 years of age. Hib was the leading cause of bacterial meningitis in the United States among children <5 years of age and a major cause of other life-threatening invasive bacterial diseases in this age group. Meningitis occurred in approximately two-thirds of children with invasive Hib disease, resulting in hearing impairment or severe permanent neurologic sequelae such as mental retardation, seizure disorder, cognitive and developmental delay, and paralysis in 15%–30% of survivors. Approximately 5% of all cases were fatal.[1]

II. Background

Before the introduction of Hib conjugate vaccines for infants in late 1990, an estimated 20,000 persons developed invasive Hib disease annually. Approximately 1 of 200 children developed invasive Hib disease before the age of 5 years, and nearly two-thirds of all cases occurred among children <18 months of age. By 1997, the incidence of all Hi invasive disease among children <5 years of age reported to the CDC declined by 97% — from 41 cases per 100,000 in 1987, to 1.3 cases per 100,000 in 1997.[2-4] Laboratory-based surveillance data from a multistate active surveillance project, which included serotype information on all invasive Hi isolates, provided direct evidence of a decline in Hib disease. From 1989 to 1997, there was a 99% reduction in serotype b disease among children <5 years of age, which coincided with the introduction and use of Hib conjugate vaccines among infants and children.[2-4]

III. Importance of rapid case identification

Rapid case identification is important for early administration of Hib vaccine or

chemoprophylaxis to household and day care classroom contacts of cases.[5]

IV. Importance of surveillance

Surveillance information is used to monitor the effectiveness of immunization programs and vaccines, and to assess progress towards disease elimination.

V. Disease reduction goals

Because of the rapid decline of Hib due to widespread immunization of infants and young children with conjugate vaccines, Hib disease among children <5 years of age in the United States has been an elimination objective proposed for the year 2010.[6]

VI. Case definition

The following case definition for *H. influenzae* (invasive disease) has been approved by the Council of State and Territorial Epidemiologists (CSTE), and was published in May 1997 (Appendix 1).[7]

Clinical description

Invasive disease caused by *H. influenzae* may produce any of several clinical syndromes, including meningitis, bacteremia, epiglottitis, or pneumonia.

Laboratory criteria for diagnosis

Isolation of *H. influenzae* from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF] or, less commonly, joint, pleural, or pericardial fluid).

Microbiology laboratories should perform serotype testing of all* H. influenzae *isolates, particularly those obtained from children <15 years of age.

Case classification

Probable: A clinically compatible case with detection of *H. influenzae* type b antigen in cerebrospinal fluid (CSF).

Confirmed: A clinically compatible case that is laboratory-confirmed.

Comment. Positive antigen test results from urine or serum samples are unreliable for diagnosis of *H. influenzae* disease.

Note: False positive results may occur from asymptomatic nasopharyngeal carriage of Hib, recent Hib vaccination, or contamination of urine specimens by cross-reacting fecal organisms. Cases identified exclusively by these methods should not be reported.

VII. Laboratory testing

Culture

Confirming a case of Hib requires culturing and isolating the organism from a normally sterile body site. Most hospital and commercial microbiologic laboratories have the ability to isolate *H. influenzae* from cultured specimens. Normally sterile site specimens for isolation of invasive *H. influenzae* include cerebrospinal fluid (CSF), blood, joint fluid, pleural effusion, pericardial effusion, peritoneal fluid, subcutaneous tissue fluid, placenta, amniotic fluid, and other normally sterile sites. Isolates should be tested also for antimicrobial susceptibility.

Serotype testing (serotyping)

Serotyping distinguishes encapsulated strains, including Hib, from unencapsulated (non-typeable) strains, which cannot be typed. The six encapsulated strains (designated a-f) have distinct capsular polysaccharides that can be differentiated by slide agglutination with specific antisera.

To monitor the occurrence of invasive Hib disease, microbiology laboratories should perform serotype testing of all *H. influenzae* isolates[8], particularly those obtained from children <15 years of age. Even though Hib disease is on the decline, laboratories should not discontinue routine serotype testing. Contact your state health department if serotyping is not available at your laboratory. The CDC Childhood and Vaccine-Preventable Diseases Laboratory will conduct serotyping for *H. influenzae* invasive disease cases among children aged <15 years. Contact the laboratory at 404-639-1379 for more information.

Antigen Detection

Because the type b capsular antigen can be detected in body fluids including urine, blood and CSF of patients, clinicians often request a rapid antigen detection test for diagnosis of Hib disease. Antigen detection may be used as an adjunct to culture, particularly in the diagnosis of patients who have received antimicrobial agents before specimens are obtained for culture. If the Hib antigen is detected in the CSF and there is not a positive result from culture or sterile site, the patient should be considered a **probable case** of Hib disease and reported as such. However, this test can be positive in urine and serum of persons without invasive Hib disease (e.g., in persons with asymptomatic carriage of Hib, recently vaccinated persons, or in persons with positive urine specimens from fecal contamination), and persons who are identified exclusively by positive antigen tests in urine or serum should not be reported as cases. Because antimicrobial resistance is increasingly recognized in serious bacterial infections, isolation of the organism remains important in clinical management and bacterial cultures should be performed.

Latex agglutination (LA). A rapid and sensitive method to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid.

Counterimmunoelectrophoresis. A method to detect Hib capsular polysaccharide antigen in CSF, serum, urine, pleural fluid, or joint fluid, which is more specific but is less sensitive than LA, takes longer, and is more difficult to perform.

Subtyping

For epidemiologic purposes, subtyping on the basis of outer membrane proteins, lipopolysaccharides, or enzyme electrophoresis can be performed, but is not widely available. The State Health Department may direct questions about subtyping to the CDC Childhood and Vaccine-Preventable Diseases Laboratory at 404-639-1379.

For additional information on laboratory support for surveillance of vaccine-preventable diseases, see Chapter 19.

VIII. Reporting

Invasive Hi disease became nationally notifiable in 1991. Each state and territory has regulations or laws governing the reporting of diseases and conditions of public health importance (Appendix 2).[9] These regulations/laws list the diseases that are to be reported and describe those persons or groups who are responsible for reporting, such as health care providers, hospitals, laboratories, schools, day care facilities, and other institutions. Contact your state health department for reporting requirements in your state.

Reporting to CDC

A provisional report of probable and confirmed cases should be sent to the National Notifiable Disease Surveillance System by the state health department via the National Electronic Telecommunications System for Surveillance (NETSS) within 14 days of the initial report to the state or local health department. Reporting should not be delayed because of incomplete information or lack of confirmation.

The National Bacterial Meningitis and Bacteremia Case Report form (Appendix 6) can be used to collect information on each case. Many state health departments have the technology available to send this detailed case report information to CDC through NETSS by using supplemental data entry screens. Although completion of supplemental information forms for all cases of disease is ideal, it is especially important that such information be sent to CDC for cases of invasive Hi disease among children <15 years of age.

Information to collect

The following data are epidemiologically important and should be collected in the course of case investigation. Additional information may be collected at the direction of the state health department.

- Demographic information

- Vaccination status (for type b or unknown serotype infections only) including
  - —Date of each Hib immunization
  - —Manufacturer and lot number of vaccine(s) used

- Attendance in day care

- Clinical details, including
  - —Type of disease syndrome (e.g., meningitis, bacteremia, epiglottitis, arthritis, osteomyelitis, pericarditis, empyema, cellulitis, abscess)
  - —Date first positive culture obtained
  - —Outcome of illness (died or survived)

- Laboratory information including
  - —Serotype of isolate
  - —Specimen source from which organism isolated (e.g.,blood, CSF, pleural fluid, peritoneal fluid, pericardial fluid, joint fluid, placenta, amniotic fluid, other normally sterile site)

- Microbial susceptibility

IX. Vaccination

Table 1 lists the Hib conjugate vaccines which are currently available.

As of September 1999, four combination vaccines including Hib conjugate vaccine have been licensed by the FDA following immunogenicity and safety studies (Table 2). These combination vaccines decrease the number of injections needed for protection against vaccine-preventable diseases, however, DTaP is the preferred vaccine formulation for all doses in the series.

The recommended schedule for Hib conjugate vaccine administration among previously unvaccinated children is given in Table 3.[5] Based on the recommended schedule, infants should receive three primary doses of Hib conjugate vaccine with HbOC or PRP-T at ages 2, 4, and 6 months, or two primary doses PRP-OMP at 2 and 4 months. A booster dose should be administered at age 12-15 months with any of the conjugate vaccines. Any type of licensed Hib vaccine may be used interchangeably to complete the series, and the number of doses needed to complete the series is determined by the type of vaccine used (i.e., 4 doses if either HbOC or PRP-T is used at least once).[10]

X. Enhancing surveillance

Elimination of childhood Hib disease requires participation by all levels of the health-care system in rapid identification, assessment, and prompt reporting of all cases and optimal use of these data to prevent disease among un- or under-vaccinated populations. The activities listed below can improve the detection and reporting of cases and improve the comprehensiveness and quality of reporting.

See Chapter 16, "Enhancing Surveillance," for additional recommendations for enhancing surveillance of vaccine-preventable diseases.

Assuring that all isolates from children are serotyped. Because Hib vaccines protect against serotype b organisms only, serotype should be determined and reported for all *Haemophilus influenzae* isolates. It is particularly important that serotype be reported for cases among children <15 years of age. This information is used to determine whether a case indicates a vaccine failure (i.e., a vaccinated person who gets the disease) or a failure to vaccinate. The state public health laboratory or another reference laboratory should be available for serotype testing of *H. influenzae* isolates. Hospital laboratories unable to perform serotype testing should forward all Hi isolates for serotyping to such a laboratory. Contact your state health department if serotyping is not available.

Monitoring surveillance indicators. Regular monitoring of surveillance indicators including reporting dates, time intervals between diagnosis and reporting, and completeness of reporting may identify specific areas of the surveillance system that need improvement. Important indicators to evaluate the completeness and overall quality of the surveillance system include:

- Proportion of Hi cases with known serotype among children < 5 or < 15 years of age.

- Proportion of Hib cases with complete vaccination information (date, manufacturer, lot number).

Monitoring the incidence of invasive disease due to non-type b *H. Influenzae*. Data from active surveillance sites suggest an expected rate of invasive disease due to non-type b *H. influenzae* to be $\geq$1.5 per 100,000 children aged <5 years.[11] This rate may be used as a surveillance indicator for monitoring the quality or reporting *H. influenzae* type b invasive disease cases. Although limited data are available on temporal and geographic variability in incidence of non-type b invasive diseases, use of this surveillance indicator is encouraged.

XI. Case investigation

Laboratory, hospital, and clinic records should be reviewed during case investigation by health department personnel in order to collect important information such as serotype, immunization status, dates of vaccination, vaccine lot numbers, and clinical illness description and outcome. The National Bacterial Meningitis and Bacteremia Case Report form may be used as a guide for collecting demographic and epidemiologic information in a case investigation (Appendix 6).

Investigating contacts. Identification of young children who are household or day care classroom contacts of cases and assessment of their vaccination status may help identify persons who should receive antimicrobial prophylaxis and who need to be immunized.

The Advisory Committee on Immunization Practices recommends that because children who attend day care are at increased risk for Hib disease, efforts should be made to ensure that all day care attendees <5 years of age are fully vaccinated.[5] A child who has recovered from invasive Hib disease should receive Hib conjugate vaccine because natural infection does not always result in the development of antibodies protective against the *H. influenzae* capsular polysaccharide (PRP). For household contacts of a person with invasive Hib disease, no rifampin chemoprophylaxis is indicated if all persons are ≥5 years of age, or if children <5 years of age are fully vaccinated according to Table 3. In households with one or more infants <12 months of age, with a child 2-3 years of age who is inadequately vaccinated, or with an immunocompromised child, all household contacts, including the index case-patient, should receive rifampin prophylaxis. The recommended dose is 20 mg/kg as a single daily dose (maximal daily dose 600 mg) for 4 days. Neonates (<1 month of age) should receive 10 mg/kg once daily for 4 days.[5] ❖

Table 1. Hib conjugate vaccines currently available		
Licensed vaccine	**Trade name**	**Manufacturer/Distributor**
PRP-D	ProHIBit®	Connaught Laboratories
HbOC	HibTITER®	Praxis/Lederle Laboratories
PRP-T	ActHIB® OmniHIB®	Pasteur Merieux/Connaught SmithKline Beecham
PRP-OMP	PedvaxHIB®	Merck & Company

Table 2. Combination vaccines containing Hib conjugate vacccines		
Licensed vaccine	**Trade name**	**Manufacturer/Distributor**
HbOC + DTP	TETRAMUNE®	Lederle Laboratories
PRP-T + DTP*	--------	Pasteur Merieux/ Connaught
PRP-T + DTaP¶	TriHIBit®	Connaught Laboratories
PRP-OMP + HepB	COMVAX™	Merck & Company

*ACTHib® and DTP are combined in single syringe for administration.
¶ As of July 15, 1997, TriHIBit® was licensed for use only for the fourth dose of the DTaP and Hib vaccination series among children 15-18 months of age, and should be administered at least 6 months following the third DTP or DTaP dose.

Table 3. Recommended schedule for Hib conjugate vaccine administration among previously unvaccinated children.

Vaccine	Age (months) at first vaccination	Primary series	Booster
HbOC/PRP-T	2-6	3 doses, 2 mos apart	12-15 mos
	7-11	2 doses, 2 mos apart	12-18 mos
	12-14	1 dose	2 mos later
	15-59	1 dose	NR*
PRP-OMP	2-6	2 doses, 2 mos apart	12-15 mos
	7-11	2 doses, 2 mos apart	12-18 mos
	12-14	1 dose	2 mos later
	15-59	1 dose	NR*
PRP-D	15-59	1 dose	NR*

* Not required.

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